Baseline characteristics of the 4011 patients recruited into the 'Efficacy of Nitric Oxide in Stroke' (ENOS) trial

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ENOS Investigators†

Background **High blood pressure is common in acute stroke and associated with a worse functional outcome. Many patients who present with acute stroke are taking prescribed antihypertensive therapy before their stroke.**

Aims **ENOS tested whether lowering blood pressure and continuing pre-stroke antihypertensive therapy are each safe and effective.**

Methods **This study is an international multi-centre prospective randomized single-blind blinded-endpoint parallel-group partial-factorial controlled trial of transdermal glyceryl trinitrate (a nitric oxide donor, given for seven-days) vs. no glyceryl trinitrate, and of continuing vs. stopping (temporarily for seven-days) pre-stroke antihypertensive drugs if relevant, in patients with acute ischaemic stroke or intracerebral haemorrhage and high systolic blood pressure (140–220 mmHg).**

Results **Recruitment ran from July 2001 to October 2013. Four thousand eleven patients [2097 (52·3%) in the continue/stop arm] were recruited from 173 sites across 23 countries in 5 continents (Asia 14%, Continental Europe 16%, UK 64%). Baseline characteristics include: mean age 70 (standard deviation 12) years; male 57%; mean time from stroke to recruitment 26 (13) h; mean severity (Scandinavian Stroke Scale) 34 (13) of 58; mean blood pressure 167 (19)/90 (13) mmHg; ischaemic stroke 83%; and intracerebral haemorrhage 16%. The main trial results will be presented in May 2014. The results will also be presented in updated Cochrane systematic reviews and included in individual patient data meta-analyses of all relevant randomized controlled trials.**

Conclusion **ENOS is a large completed international trial of blood pressure management in acute stroke and includes patients representative of many stroke services worldwide.**

Key words: acute stroke, antihypertensive drugs, blood pressure, glyceryl trinitrate, nitric oxide, randomized controlled trial

Introduction

High systolic blood pressure (SBP > 140 mmHg) is present in 70% or more of patients with acute ischaemic stroke (IS) and intracerebral haemorrhage (ICH) (1). Affected patients have a worse outcome, whether judged as early recurrence, death within a few weeks, or combined death and dependency after several months (1–4). Lowering blood pressure (BP) might therefore reduce these events and improve functional outcome, provided that cerebral perfusion is not critically reduced. As a result of this uncertainty, guidelines are not definitive about the management of BP in acute stroke (5). The recent observation that intensive lowering of BP in hyperacute ICH may improve outcome (6) raises the possibility that optimal BP management may vary between IS and ICH.

Nitric oxide (NO) donors are candidate treatments for acute stroke; NO is a cerebral and systemic vasodilator, modulates vascular and neuronal function, and inhibits apoptosis (7). Preclinical studies of cerebral ischemia have found that NO donors reduce stroke lesion size and improve regional cerebral blood flow (CBF) and functional outcome (8). Five small clinical studies of NO donors in patients with acute or recent stroke have been performed. Intravenous sodium nitroprusside reduced BP without altering CBF and exhibited antiplatelet effects (thereby precluding its use in ICH) (9). Four pilot trials of transdermal glyceryl trinitrate (GTN) found that it lowered BP by approximately 8% (albeit with tachyphylaxis developing over the first week of treatment), did not alter platelet function (and so could be given in ICH), did not alter middle cerebral artery blood flow velocity or regional CBF, improved aortic vascular compliance, and could be given to patients with dysphagia (10–13). In one small trial, functional outcome was improved with GTN when given within 4 h of stroke onset (13). Overall, GTN was feasible to administer and appeared safe (10–18).

In addition to the question of whether BP should be lowered during the acute phase of stroke, a separate question is whether antihypertensive agents taken at home before the stroke should be continued or stopped during the acute and sub-acute period after stroke (19). The COSSACS trial intended to address this question in 2900 patients but low recruitment meant that only 763 patients were able to be recruited (20,21). This question remains clinically important and was incorporated into ENOS for relevant patients.

Methods

Eligibility and consent

The full inclusion and exclusion criteria are given in the published protocol (22) and in the latest version of the protocol (Supporting Information Appendices S1 and S2). Adult patients with acute ischaemic or haemorrhagic stroke were eligible if they were previously independent [modified Rankin Scale (mRS) 0–2], conscious (Glasgow Coma Scale > 8), had residual limb weakness, had SBP between 140–220 mmHg, and were within 48 h of onset. The investigator had to be uncertain about whether BP should be lowered in acute stroke and whether pre-stroke antihypertensive

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Conflict of interest: P. M. W. Bath: Chief Investigator of GTN-1/2/3 and RIGHT pilot trials; lead author of three relevant Cochrane reviews: nitric oxide, BASC-1, and BASC-2; ENOS grant applicant. E. Berge: Chief Investigator of SCAST. K. R. Lees: Chief Investigator of IMAGES; ENOS grant co-applicant. S. Pocock: ENOS grant co-applicant. J. M. Wardlaw: Co-chief Investigator of IST-3 and an ENOS grant co-applicant. D. Whynes: ENOS grant co-applicant. The remaining authors have no relevant declarations.

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medication (if being taken) should be continued or stopped temporarily. Patients gave written informed consent prior to enrollment; if they lacked capacity (e.g. due to drowsiness, dysphasia, or confusion) then a relative could give proxy consent. Proxy consent by an independent physician was also permissible if allowed by local site regulations. Patients had a computed tomography or magnetic resonance imaging (MRI) brain scan pre- or soon after randomization, and a repeat brain scan at seven-days, where possible or if there was any neurological deterioration.

Randomization and data collection

After informed consent had been obtained, the clinician used the secure web-based randomization system to enter a patient into the study. The system recorded baseline characteristics of the patients, validated data with range and consistency checks, and then allocated the patient to treatment. To achieve optimal baseline matching between treatment groups and ensure concealment of allocation, randomization incorporated stratification (country, stroke type, use of pre-stroke antihypertensive drugs) and minimization (on baseline prognostic factors, as highlighted in Table 1); the minimization algorithm included a random element (simple randomization) in 5% of patients. Stratification and minimization allow for improved matching at baseline, minimization increases statistical power (24), and simple randomization reduces predictability. Following randomization, the investigator was informed of the patient's treatment allocation: to GTN or no GTN for one-week and if relevant to continue or stop pre-stroke antihypertensive drugs for one-week. The minimization variables will be used for adjustment of the primary and secondary analyses (25), as recommended (24).

Outcomes

The primary and main secondary outcomes were collected centrally at day 90 by an assessor in each country who was blinded to treatment. In most territories, they first contact the general practitioner to check that the patient is still alive, and then telephone the patient (and carer as appropriate). Where telephone contact cannot be made, outcome information was collected using a postal questionnaire. Final stroke diagnosis was determined from the local investigator diagnosis and blinded central scan adjudication of the brain imaging data. The primary outcome was the mRS at day 90; secondary outcomes include early events at day 7; measures of disability, cognition, mood, and quality of life at day 90; death; and the effect of BP lowering on infarct swelling at 7 days in patients with follow-up scans (22).

Use of the Internet

The trial was the first acute stroke trial in the world to use the Internet to randomize and collect data in real time online:

- Trial website: http://www.enos.ac.uk/
- Secure website for real-time data entry, validation, and randomization: http://www.nottingham.ac.uk/~nszwww/enos/enostrialdb/
- Demo website for investigators to practice data entry: https://www.nottingham.ac.uk/~nszwww/enos/enostrialdb-demo/enos_login.php (log-in: demoinv1, password: nottingham; pin: 8888)

Progress with the study and modifications to the design

Planning for ENOS commenced in 2000 following the results of the first two pilot randomized controlled trials of GTN (10,11). The trial has had multiple phases and funding:

- Initial phase (July 2001 to March 2004): funding from Division of Stroke, University of Nottingham UK and a bequest from the Reichstadt Family. Two hundred twenty-one patients recruited.
- Start-up phase (April 2004 to October 2006): funding from the Bupa Foundation, with additional support from the Hypertension Trust. The Singapore A Star funded an MRI substudy in Singapore (26). Two hundred ninety-nine patients recruited.
- Main phase (November 2006 to October 2013, with funding through to end April 2014): funding from the UK Medical Research Council [latterly administered by the National Institute for Health Research (NIHR) Efficacy and Mechanism Evaluation program]. Three thousand four hundred ninety-one patients recruited. Initially, the aim was to recruit a total of 5000 patients, as published in the protocol in 2006 (22). A revised sample size of at least 3500 patients was set in April 2009 (25).

Throughout the trial, six protocol amendments were made covering multiple issues. The key one was to optimize the method of analysis of the primary outcome, which allowed a reduction in sample size and is important as the recruitment rate was not compatible with reaching the originally planned total of 5000 patients. Research in the early and mid-2000s have shown that a binary analysis of the mRS (0–2 vs. 3–6) was sub-optimal and that statistical power could be increased by incorporating all seven individual mRS scores in the analysis and then comparing the distribution in mRS between the treatment groups (27). This approach is now recommended by the European Stroke Organisation (28). A further and additional increase in statistical power could be achieved by incorporating key prognostic baseline variables as covariates (29). These approaches were similar to findings from other groups (30–32).

Hence, the primary analysis of the mRS in ENOS will utilize the shift approach, as analyzed using ordinal logistic regression, with adjustment for covariates, with comparison between treatment groups (GTN/no GTN; continue/stop pre-stroke BP medications). The overall proposal to change the method of analysis of the primary outcome from binary to ordinal was first presented to, and agreed by, the Trial Steering Committee in January 2008 and confirmed in 2009; this decision was made without knowledge of the unblinded data. A draft statistical analysis plan (SAP), highlighting this change, was posted on the trial website in April 2009. The final SAP was submitted for publication in 2013 prior to the planned unblinding of the data in early 2014 (25).

The trial is supervised by a Trial Steering Committee and International Advisory Committee, run by a trial management committee (based in Nottingham, UK), and was monitored by an independent data monitoring committee (DMC) (Supporting Information Appendix S3). By the end of recruitment, the DMC met and assessed safety and efficacy on 23 occasions. Independent experts adjudicated brain scans and serious adverse events, and were blinded to treatment.

Table 1 Clinical characteristics at randomization

Variable	All patients (GTN/No GTN)	Continue-stop	Not in continue-stop
No. of patients (%)	4011 (100)	2097 (52·3)	1914 (47·7)
Age (years)			
Mean (SD)*	70·3 (12·2)	72·9 (11·2)	67·4 (12·6)
18 (%)§	0 (0·0)	0 (0·0)	0 (0·0)
18–40 (%)	39 (1·0)	11 (0·5)	28 (1·5)
41–50 (%)	239 (6·0)	68 (3·2)	171 (8·9)
51–60 (%)	606 (15·1)	237 (11·3)	369 (19·3)
61–70 (%)	986 (24·6)	458 (21·8)	528 (27·6)
71–80 (%)	1284 (32·0)	755 (36·0)	529 (27·6)
81–90 (%)	758 (18·9)	511 (24·4)	247 (12·9)
91–100 (%)	99 (2·5)	57 (2·7)	42 (2·2)
>100 (%)	0 (0·0)	0 (0·0)	0 (0·0)
Gender			
Male (%)*	2297 (57·3)	1068 (50·9)	1229 (64·2)
Female (%)	1714 (42·7)	1029 (49·1)	685 (35·8)
Geographical region†			
Africa	148 (3·7)	71 (3·4)	77 (4·0)
America, north	33 (0·8)	14 (0·7)	19 (1·0)
Asia, east	107 (2·7)	41 (2·0)	66 (3·4)
Asia, south	267 (6·7)	74 (3·5)	193 (10·1)
Asia, south-east	185 (4·6)	87 (4·1)	98 (5·1)
Australasia	79 (2·0)	51 (2·4)	28 (1·5)
British Isles	2555 (63·7)	1354 (64·6)	1201 (62·7)
Europe, mainland	637 (15·9)	405 (19·3)	232 (12·1)
Time of stroke randomization (hours)			
Mean (SD)*	26·0 (12·9)	25·6 (12·9)	26·4 (12·8)
Median [IQR]	26·0 [20·6]	25·7 [20·0]	26·5 [20·6]
<1 (%)§	0 (0·0)	0 (0·0)	0 (0·0)
1–6 (%)	273 (6·8)	143 (6·8)	130 (6·8)
7–12 (%)	438 (10·9)	241 (11·5)	197 (10·3)
13–18 (%)	470 (11·7)	267 (12·7)	203 (10·6)
19–24 (%)	597 (14·9)	304 (14·5)	293 (15·3)
25–36 (%)	1203 (30·0)	629 (30·0)	574 (30·0)
37–48 (%)	1015 (25·3)	509 (24·3)	506 (26·4)
>48 (%)§	15 (0·4)	4 (0·2)	11 (0·6)
Hemodynamics			
Systolic BP (mmHg)			
Mean (SD)*	167·2 (19·0)	167·1 (18·8)	167·4 (19·1)
<140 (mmHg)	168 (4·2)	85 (4·1)	83 (4·3)
140–160 (mmHg)	1439 (35·9)	764 (36·4)	675 (35·3)
161–180 (mmHg)	1434 (35·8)	739 (35·2)	695 (36·3)
181–200 (mmHg)	723 (18·0)	379 (18·1)	344 (18·0)
201–220 (mmHg)	238 (5·9)	125 (6·0)	113 (5·9)
>220 (mmHg)	9 (0·2)	5 (0·2)	4 (0·2)
Diastolic BP, mean (mmHg)	89·5 (13·1)	88·3 (13·1)	90·9 (13·1)
Heart rate, mean (bpm) (n = 4007)	77·5 (14·7)	77·1 (15·2)	77·9 (14·2)
Atrial fibrillation (%)			
Current/previous history	571 (14·2)	459 (21·9)	112 (5·9)
On ECG	665 (16·6)	487 (23·2)	178 (9·3)
Any (%)	762 (19·0)	566 (27·0)	196 (10·2)
Qualifying event (%)*¶			
Ischaemic stroke	3342 (83·3)	1832 (87·4)	1510 (78·9)
Intracerebral haemorrhage	629 (15·7)	246 (11·7)	383 (20·0)
Stroke type unknown	1 (0·1)	1 (0·1)	0 (0·0)
Not stroke	39 (1·0)	18 (0·9)	21 (1·1)
Unknown (no form submitted)	0 (0·0)	0 (0·0)	0 (0·0)
Scandinavian Stroke Scale (/58) Σ			
Mean (SD)*	33·7 (13·2)	32·9 (13·4)	34·6 (12·8)
Median [IQR]	36·0 [20·0]	35·0 [21·0]	37·0 [19·0]
51–58	337 (8·4)	165 (7·9)	172 (9·0)
41–50	1134 (28·3)	558 (26·6)	576 (30·1)

Table 1 Continued

Variable	All patients (GTN/No GTN)	Continue-stop	Not in continue-stop
31–40	1014 (25·3)	534 (25·5)	480 (25·1)
21–30	778 (19·4)	399 (19·0)	379 (19·8)
11–20	453 (11·3)	270 (12·9)	183 (9·6)
0–10	295 (7·4)	171 (8·2)	124 (6·5)
NIHSS (/42), calculated (23)	11·2 (5·7)	11·5 (5·8)	10·8 (5·5)
Glasgow Coma Scale [/15]			
Mean (SD)	14·2 (1·5)	14·1 (1·6)	14·3 (1·5)
Median [IQR]	15·0 [1·0]	15·0 [1·0]	15·0 [1·0]
15	2782 (69·4)	1370 (65·3)	1412 (73·8)
14	432 (10·8)	262 (12·5)	170 (8·9)
13	175 (4·4)	104 (5·0)	71 (3·7)
12	219 (5·5)	128 (6·1)	91 (4·8)
11	197 (4·9)	116 (5·5)	81 (4·2)
10	120 (3·0)	71 (3·4)	49 (2·6)
9	86 (2·1)	46 (2·2)	40 (2·1)
<9§	0 (0·0)	0 (0·0)	0 (0·0)
OCSP classification (%)			
Total anterior*	1209 (30·1)	697 (33·2)	512 (26·8)
Partial anterior	1251 (31·2)	702 (33·5)	549 (28·7)
Lacunar	1397 (34·8)	624 (29·8)	773 (40·4)
Posterior	154 (3·8)	74 (3·5)	80 (4·2)
Medical history (%)			
Hypertension	2607 (65·0)	1994 (95·1)	613 (32·0)
Treated hypertension†	2138 (53·3)	2086 (99·5)	52 (2·7)
Hyperlipidemia	1098 (27·4)	808 (38·5)	290 (15·2)
Diabetes mellitus	699 (17·4)	484 (23·1)	215 (11·2)
Stroke	594 (14·8)	416 (19·8)	178 (9·3)
Transient ischaemic attack	544 (13·6)	352 (16·8)	192 (10·0)
Ischaemic heart disease	669 (16·7)	523 (24·9)	146 (7·6)
Peripheral arterial disease	117 (2·9)	77 (3·7)	40 (2·1)
Family history of young stroke, first degree relative (n = 3878)	229 (5·9)	132 (6·5)	97 (5·2)
Smoking (%) (n = 3846)			
Current	945 (24·6)	363 (18·2)	582 (31·5)
Past	1222 (31·8)	689 (34·5)	533 (28·9)
Never	1679 (43·7)	948 (47·4)	731 (39·6)
Alcohol, median (units per week)			
>21	294 (7·3)	104 (5·0)	190 (9·9)
<21	1582 (39·4)	793 (37·8)	789 (41·2)
None	1840 (45·9)	1031 (49·2)	809 (42·3)
Premorbid modified Rankin Scale (mRS) [/2]			
mRS 0	2985 (74·4)	1413 (67·4)	1572 (82·1)
mRS 1	551 (13·7)	360 (17·2)	191 (10·0)
mRS 2	473 (11·8)	322 (15·4)	151 (7·9)
mRS > 2§	2 (0·1)	2 (0·1)	0 (0·0)
Medications (%)			
BP lowering			
Angiotensin-converting enzyme inhibitor	1010 (25·2)	999 (47·6)	11 (0·6)
Angiotensin receptor antagonist	348 (8·7)	337 (16·1)	11 (0·6)
Renin inhibitor	4 (0·1)	4 (0·2)	0 (0·0)
ß-receptor antagonist	838 (20·9)	820 (39·1)	18 (0·9)
Calcium channel blocker	742 (18·5)	725 (34·6)	17 (0·9)
Diuretic	755 (18·8)	735 (35·1)	20 (1·0)
α-receptor antagonist	150 (3·7)	146 (7·0)	4 (0·2)
Centrally acting	33 (0·8)	32 (1·5)	1 (0·1)
Other	23 (0·6)	23 (1·1)	0 (0·0)
BP tablets taken before onset			
Mean (SD)	1·0 (1·1)	1·8 (0·9)	0·0 (0·3)
Median [IQR]	1·0 [2·0]	2·0 [1·0]	0·0 [0·0]
Mode	0·0	1·0	0·0
0 (%)	1873 (46·7)	11 (0·5)	1862 (97·3)
1 (%)	949 (23·7)	915 (43·6)	34 (1·8)

Table 1 Continued

Variable	All patients (GTN/No GTN)	Continue-stop	Not in continue-stop
2 (%)	738 (18·4)	729 (34·8)	9 (0·5)
3 (%)	341 (8·5)	335 (16·0)	6 (0·3)
4 (%)	96 (2·4)	93 (4·4)	3 (0·2)
5 (%)	13 (0·3)	13 (0·6)	0 (0·0)
6 (%)	1 (0·1)	1 (0·1)	0 (0·0)
7 (%)	0 (0·0)	0 (0·0)	0 (0·0)
Lipid lowering (n = 3972)	1217 (30·6)	882 (42·5)	335 (17·7)
Nitrate	154 (3·8)	136 (6·5)	18 (0·9)
Side of lesion, right (%) (n = 4003)	2086 (52·1)	1074 (51·3)	1012 (53·0)
TOAST classification (%) (n = 3342)‡			
Cardioembolic	717 (21·5)	507 (27·7)	210 (13·9)
Large vessel	742 (22·2)	417 (22·8)	325 (21·5)
Small vessel/lacunar	1276 (38·2)	626 (34·2)	650 (43·0)
Mixed	113 (3·4)	74 (4·0)	39 (2·6)
Unknown	662 (19·8)	330 (18·0)	332 (22·0)
Temperature (°C) (n = 3894)	36·6 (0·7)	36·5 (0·7)	36·6 (0·6)
Glucose (mmol/l) (n = 3845)	7·4 (3·0)	7·5 (3·0)	7·3 (3·1)
Feeding (%)			
Normal diet	1738 (43·3)	814 (38·8)	924 (48·3)
Soft diet	942 (23·5)	509 (24·3)	433 (22·6)
Nasogastric fed	225 (5·6)	103 (4·9)	122 (6·4)
PEG-fed	7 (0·2)	7 (0·3)	0 (0·0)
Intravenous/subcutaneous fluids	726 (18·1)	426 (20·3)	300 (15·7)
Nil	373 (9·3)	238 (11·3)	135 (7·1)
Thrombolysis, given*	425 (10·6)	248 (11·8)	177 (9·2)

Data are number (%), median [interquartile range], or mean (standard deviation).
*Minimization variable; †stratification variable; ‡may exceed 100%; §protocol violation; ¶final diagnosis from hospital event form at discharge or death.
Σ Scandinavian Stroke Scale (SSS): ranges from 0 (coma with quadriplegia) to 58 (normal neurological status); the similar National Institutes of Health Stroke Scale moves in the opposite direction ranging from 0 (normal neurological status) to 42 (coma with quadriplegia).
BP, blood pressure; bpm, beats per minute; ECG, ; GTN, glyceryl trinitrate; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; OCSP, Oxfordshire Community Stroke Project; PEG, percutaneous endoscopic gastrostomy; SD, standard deviation; TOAST, Trial of ORG 10172 in Acute Stroke Treatment.

Results

Trial delivery

Recruitment progressed with a start-up phase in a limited number of sites, and then expanded to a main phase (Figure 1a,b). As with any large international, investigator driven trial with limited funding, ENOS has suffered from a number of issues although none materially affected data integrity or validity. These include problems with blinding, recruitment, randomization, inappropriate treatment, and data loss (Supporting Information Appendix S4).

Baseline characteristics

Four thousand eleven patients were recruited from 173 sites (Table 2, Supporting Information Appendix S3) across 23 countries in 5 continents (Asia 14%, continental Europe 16%, UK 64%) over the 12-year period from July 20, 2001 to October 14, 2013. Two thousand ninety-seven (52·3%) of these patients were also recruited into the continue/stop arm of the trial. The majority of patients were entered into the trial over the latter part of the trial, for example, from start of 2008: GTN/no GTN 3182 (79%), continue/stop 1711 (82%) (Figure 1a,b). Around two-thirds of patients were recruited from one-third of sites (Figure 2a,b). Three sites (Dublin, Eire; Ragama, Sri Lanka; Nottingham, UK) ran temporary screening logs at some point in the trial; altogether, of 174 patients screened, 30 (17%) were enrolled.

The baseline characteristics (Table 1) are presented as number (%), median [interquartile range], or mean (standard deviation). Key features include: mean age 70·3 (standard deviation 12·2) years; male 57·3%; mean time to recruitment 26·0 (12·9) h; mean severity (Scandinavian Stroke Scale) 33·7 (13·2) of maximum 58 (estimated National Institutes of Health Stroke Scale 11 (35)); mean BP 167·2 (19·0)/89·5 (13·1) mmHg; IS 83·3%; ICH 15·7%; stroke of unknown type 0·1%; and nonstroke 1·0%. In comparison with patients not taking antihypertensive agents prior to their stroke, those patients on pre-stroke BP drugs were older, more likely to be female, have atrial fibrillation, have had a previous stroke and/or ischaemic heart disease, and present with an IS.

Table 3 shows univariate relationships between a number of key baseline factors, including year of enrollment; as the trial progressed, average age increased. In contrast, the proportion of men, proportion of patients with haemorrhage, and severity, SBP, and time to recruitment decreased. In other univariate analyses, increasing age was associated with an increase in time to recruitment, a decline in the proportion of males and patients with haemorrhage, and reduced severity and SBP; males had more severe stroke and haemorrhages but had a reduced SBP and time

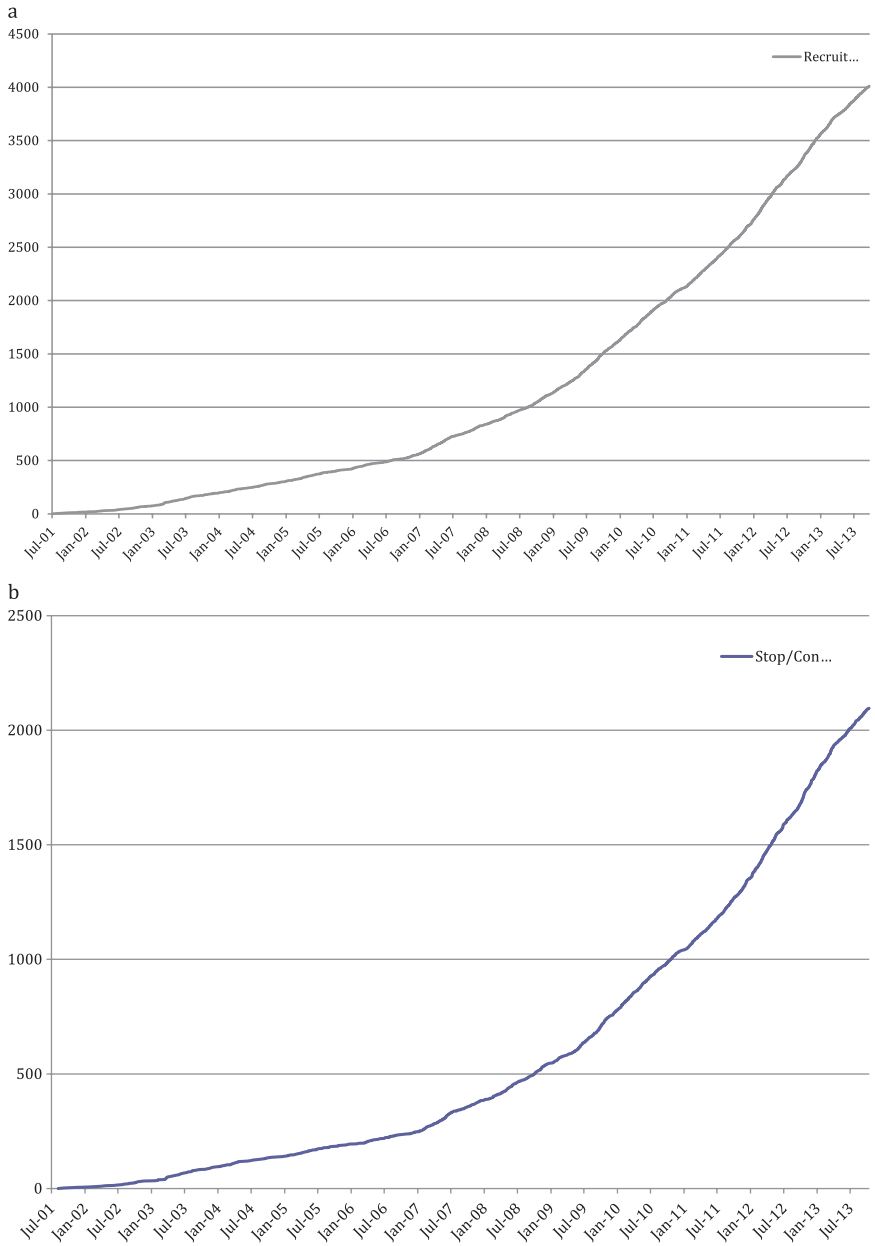

Fig. 1 (a) Recruitment curve by time for GTN/no GTN. (b) Recruitment curve by time for continue/stop pre-stroke antihypertensive drugs. GTN, glyceryl trinitrate.

to recruitment; and increasing stroke severity was associated with a lower SBP (Table 3). ICH was associated with less severe stroke.

Reporting of results

The database will be locked and the trial unblinded and analyzed in early 2014, as per the SAP (25). The main results will be reported at the European Stroke Conference in Nice in May 2014. In parallel, separate manuscripts will be submitted addressing GTN vs. no GTN and continue vs. stop pre-stroke antihypertensive medication. Multiple prespecified secondary publications and analyses are also described in the SAP (25), including this paper.

Three Cochrane reviews will be updated with summary data from ENOS:

- Nitric oxide (14)
- Interventions for deliberately altering BP in acute stroke (BASC-1) (15)
- Vasoactive drugs for acute stroke (BASC-2) (16)

The ENOS data will also be shared with prospective individual patient data meta-analyses:

- Glyceryl trinitrate – including GTN-1/2/3, RIGHT (10–13)
- Continue vs. stop pre-stroke antihypertensive medications – including COSSACS (21)
- Blood Pressure in Acute Stroke Collaboration-3 (BASC-3) – including CATIS, COSSACS, FAST-Mag, IMAGES, INTERACT-1/2, and SCAST (6,21,36–39)

Table 2 Recruitment: number of sites and patients by region [numbers and %] and country for glyceryl trinitrate vs. none, and continue vs. stop pre-stroke antihypertensive therapy

Regions	Countries	No. of sites	No. of patients (%): GTN/no GTN	%	No. of patients (%): Continue vs. stop	%
Africa		[4]	[148]	[3·7]	[71]	[3·4]
	Egypt	4	148	3·7	71	3·4
America, north		[2]	[33]	[0·8]	[14]	[0·7]
	Canada	2	33	0·8	14	0·7
Asia, east		[3]	[107]	[2·7]	[41]	[2·0]
	China	2	103	2·6	39	1·9
	Hong Kong	1	4	0·1	2	0·1
Asia, south		[10]	[267]	[6·7]	[74]	[3·5]
	India	8	157	3·9	47	2·2
	Sri Lanka	2	110	2·7	27	1·3
Asia, south-east		[4]	[185]	[4·6]	[87]	[4·2]
	Malaysia	2	14	0·4	6	0·3
	Philippines	1	16	0·4	7	0·3
	Singapore (26)	1	155	3·9	74	3·5
Australasia		[5]	[79]	[2·0]	[51]	[2·4]
	Australia	1	8	0·2	7	0·3
	New Zealand	4	71	1·8	44	2·1
British Isles		[116]	[2555]	[63·7]	[1354]	[64·6]
	Eire	1	10	0·3	2	0·1
	UK	115	2545	63·5	1352	64·5
Continental Europe		[29]	[637]	[15·9]	[405]	[19·3]
	Denmark	3	17	0·4	7	0·3
	Georgia	3	195	4·9	152	7·3
	Greece	1	12	0·3	12	0·6
	Italy	3	33	0·8	22	1·1
	Norway	2	4	0·1	2	0·1
	Poland (33)	3	123	3·1	73	3·5
	Romania (34)	3	217	5·4	111	5·3
	Spain	2	8	0·2	5	0·2
	Sweden	4	14	0·4	10	0·5
	Turkey	5	14	0·4	11	0·5
Total	23	173	4011	100	2097	100

GTN, glyceryl trinitrate.

Table 3 Univariate correlations between baseline characteristics for age, gender, stroke severity [Scandinavian Stroke Scale (SSS)], stroke type (ischaemic, haemorrhagic), systolic blood pressure (SBP), time to randomization, and year of randomization

	Age	Gender, male	Severity (SSS)	Stroke type, bleed	SBP	Time to randomization	Year of randomization
Age	X	–0·213 (<0·001)	–0·153 (<0·001)	–0·122 (<0·001)	0·014 (0·384)	0·008 (0·627)	0·052 (0·001)
Gender	–0·213 (<0·001)	X	0·100 (<0·001)	0·044 (0·006)	–0·033 (0·037)	–0·024 (0·126)	–0·003 (0·851)
Severity	–0·153 (<0·001)	0·100 (<0·001)	X	–0·095 (0·001)	–0·057 (<0·001)	0·067 (<0·001)	–0·074 (<0·001)
Type	–0·122 (<0·001)	0·044 (0·006)	–0·095 (0·001)	X	0·085 (<0·001)	–0·026 (0·098)	–0·023 (0·144)
SBP	0·014 (0·384)	–0·033 (0·037)	–0·057 (<0·001)	0·085 (<0·001)	X	–0·022 (0·165)	–0·049 (0·002)
Time	0·008 (0·627)	–0·024 (0·126)	0·067 (<0·001)	–0·026 (0·098)	–0·022 (0·165)	X	–0·248 (<0·001)
Year	0·052 (0·001)	–0·003 (0·851)	–0·074 (<0·001)	–0·023 (0·144)	–0·049 (0·002)	–0·248 (<0·001)	X

Correlations by point biserial or Spearman's tests; data are regression coefficient (*P* value).

Discussion

With 4011 patients, ENOS is a large completed international trial of BP management in acute stroke involving both active BP lowering and the comparison of continuing vs. stopping pre-stroke antihypertensive drugs. The characteristics of the patients justify several comments. First, the wide geographical coverage and large number of recruiting sites mean that the patients are representative of those admitted to stroke services in many parts of the world. Second, most patients were recruited since 2008 and so were treated using modern clinical practice. Nevertheless, some patient characteristics did change over time reflecting differences in the types of patients being recruited by newer sites, for example, increasing age, reducing proportion of males, and time

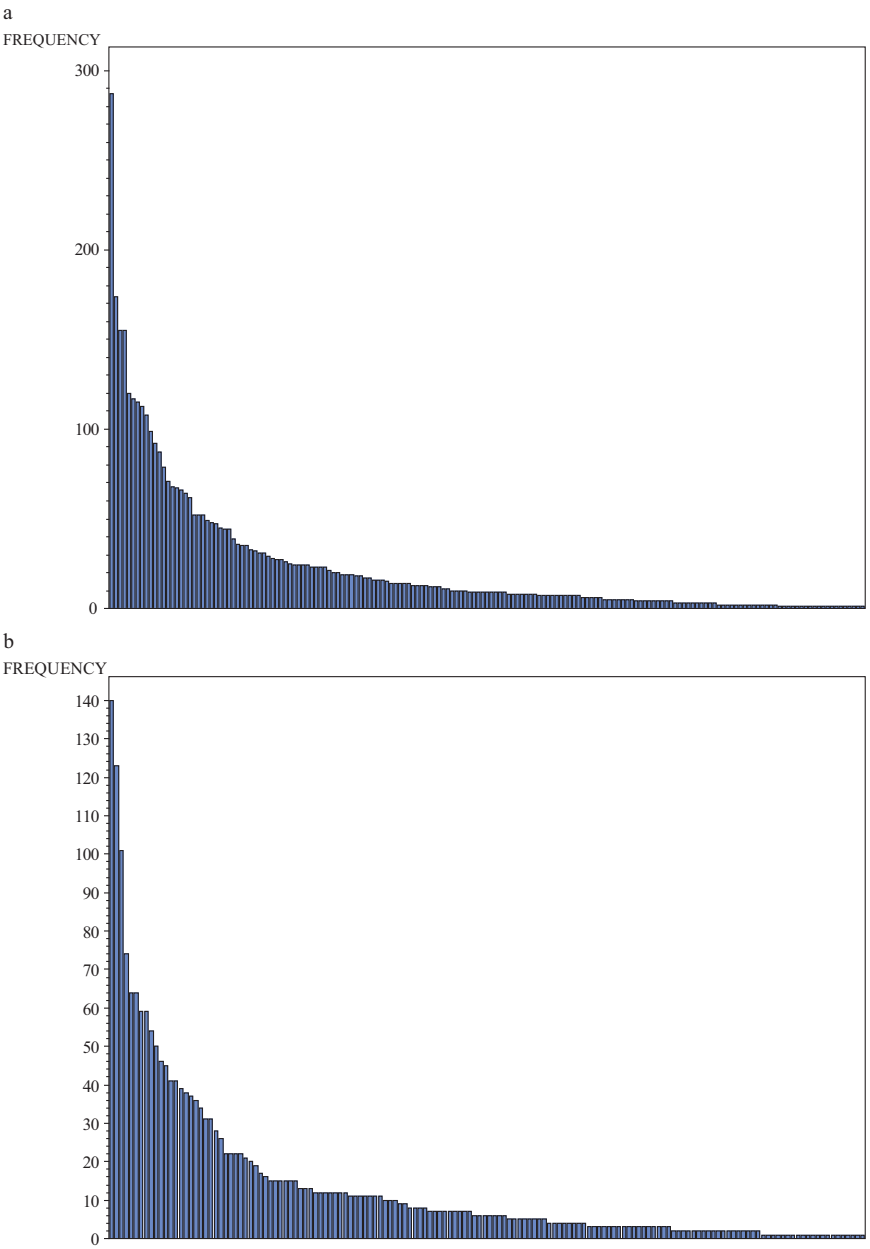

Fig. 2 (a) Bar chart showing recruitment numbers by site for GTN/no GTN. (b) Bar chart showing recruitment numbers by site for continue/stop pre-stroke antihypertensive drugs. GTN, glyceryl trinitrate.

to recruitment. Last, the observation that ICH was associated with less severe stroke, although counter-intuitive, reflects that many patients were recruited from east and south-east Asia where ICH are often sub-cortical and therefore smaller, in contrast to large cortical infarcts recruited from Europe. Additionally, the active management of severe haemorrhage, for example, BP lowering or surgery, may bias recruitment to patients with smaller hematoma.

Although ENOS is large and definitive and significant results would help drive changes in clinical practice, it will still be necessary to merge individual patient data from ENOS with other large trials of lowering BP (as planned in BASC-3) to assess fully the effects of BP management in different sub-groups of patients.

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Sites

The list of participating investigators, sites, and trial coordinating staff is given in Supporting Information Appendix S3.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1. ENOS protocol version 1·5 – current version.
Appendix S2. ENOS protocol version 1·5 – signed front page.
Appendix S3. Participating sites and investigators.
Appendix S4. Issues with the trial.